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IDENTIFICATION OF AMINO ACID SUBSTITUTIONS CORRELATED WITH REDUCED ATAZANAVIR SUSCEPTIBILITY IN PATIENTS TREATED WITH ATAZANAVIR CONTAINING REGIMENS

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RJ Colonna¹, J Friberg¹, RE Rose¹, E Lam² and N Parkin²

¹Bristol-Myers Squibb Pharmaceutical Research Laboratories, Wallingford, Conn., USA; and ²ViroLogic Inc. South San Francisco, Calif., USA

BACKGROUND: Atazanavir is a once daily HIV protease inhibitor (PI) currently in Phase III clinical trials. Previously, we have shown that atazanavir displays a distinct resistance profile relative to other PIs using a panel of clinical isolates. In this study, we sought to further describe phenotypic (PT) and genotypic (GT) patterns associated with atazanavir resistance by analysing viruses that emerged during treatment with atazanavir in clinical trials.

METHODS: PT (PhenoSense™) and GT (GeneSeq™) evaluations were performed on baseline and post-treatment isolates from 76 patients treated with atazanavir and classified as treatment failures in studies AI424-007, -008 and -009. Individual and combinations of mutations were made in recombinant viruses and their PI phenotype evaluated using a MT-2 cell infection assay.

RESULTS: Seventeen of the 76 post-treatment (24- to 104-week) isolates from patients designated as treatment failures displayed decreased susceptibilities to atazanavir ranging from 5- to 141-fold. Distinct resistance patterns appeared depending on whether study subjects were treatment naïve or experienced. Of the nine atazanavir-resistant isolates from treatment-naïve patient studies AI424-007 and AI424-008, eight had an I50L substitution and five of the eight had an I50L/A71V combination. The ninth isolate had neither substitution. These changes occurred in a variety of genetic backgrounds. Reduced susceptibility to atazanavir was not associated with loss of susceptibility to other PIs and interestingly, actually increased the susceptibility to many of them. In contrast, the eight isolates from PI-treatment experienced patients in study AI424-009 lacked the I50L substitution and nearly all isolates displayed a loss of sensitivity to other PIs in

addition to atazanavir. Atazanavir resistance in these patients required the accumulation of several additional amino acid substitutions. Recombinant viruses containing I50L and the I50L/A71V combination displayed decreased susceptibility to atazanavir and were significantly growth impaired. The I50L substitution was not found in any of the post-treatment isolates from patients in any of the three studies who remained susceptible to atazanavir and there is no evidence of cross-resistance between atazanavir and amprenavir, despite the known relationship between the I50V substitution and amprenavir resistance.

CONCLUSION: PT and GT analysis of isolates from patients treated with regimens containing atazanavir suggest that the emergence of the amino acid substitutions I50L and A71V in treatment-naïve patients may result in selective resistance to atazanavir.

PRESENTING AUTHOR: RJ Colunno

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